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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,997	10/04/2005	Kai Schiemann	MERCK-3071	6470

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EXAMINER	
MURRAY, JEFFREY H	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,997	SCHIEMANN ET AL.	
	Examiner	Art Unit	
	JEFFREY H. MURRAY	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-15 and 17-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-15 and 17-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. The final rejection mailed on January 8, 2008 has been withdrawn. The following action is issued and replaces the final action dated January 8, 2008. This action seeks to remedy additional issues with the current claim set by **withdrawing the finality** of the action. There are seventeen claims pending and seventeen claims under consideration. Claims 12 and 16 have been cancelled. This is the third action on the merits. The application relates generally to chromenoneindole derivatives of the Formula I and finding novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

Withdrawn Rejections/Objections

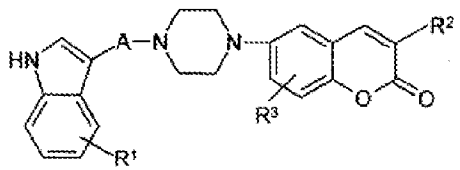
2. Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

Claim Rejections - 35 USC § 112, 1st paragraph

3. Claim 1-11, 13-15 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making “derivatives, solvates, or stereoisomers” of the claimed compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

4. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

1) *Amount of guidance provided by Applicant.* The Applicant has demonstrated within the application how to make chromenoneindoles. Within the application, Claim 1 states a general formula (I):



There is no working example of any "derivatives, solvates or stereoisomers" formed. The claims are drawn to "derivatives, solvates or stereoisomers" yet none of the numerous examples presented produced any "derivatives, solvates or stereoisomers." These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However...there is no evidence that such compounds exist...the examples of the '881 patent do not produce the postulated compounds...there is...no evidence that such compounds even exist." The same circumstance appears to be true here. There is

no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

2) Unpredictability in the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Chemistry is unpredictable. *See In Re Marzocchi and Horton* 169 USPQ at 367 paragraph 3:

> "Most non-chemists would probably be horrified if they were to learn how many attempted syntheses fail, and how inefficient research chemists are. The ratio of successful to unsuccessful chemical experiments in a normal research laboratory is far below unity, and synthetic research chemists, in the same way as most scientists, spend most of their time working out what went wrong, and why. Despite the many pitfalls lurking in organic synthesis, most organic chemistry textbooks and research articles do give the impression that organic reactions just proceed smoothly and that the total synthesis of complex natural products, for instance, is maybe a labor-intensive but otherwise undemanding task. In fact, most syntheses of structurally complex natural products are the result of several years of hard work by a team of chemists, with almost every step requiring careful optimization. The final synthesis usually looks quite different from that originally planned, because of unexpected difficulties encountered in the initially chosen synthetic sequence. Only the seasoned practitioner who has experienced for himself the many failures and frustrations which the development (sometimes even the repetition) of a synthesis usually implies will be able to appraise such work .....Chemists tend not to publish negative results, because these are, as opposed to positive results, never definite (and far too copious)" Dorwald F. A. *Side Reactions in Organic Synthesis*, 2005, Wiley: VCH, Weinheim pg. IX of Preface.

The scope of “solvate” is not adequately enabled or defined. Applicants provide no guidance as how the compounds are made more active *in vivo*. Solvates cannot be

predicted and therefore are not capable of being claimed if the applicant cannot properly enable a particular solvate.

> "Predicting the formation of solvates or hydrates of a compound and the number of molecules of water or solvent incorporated into the crystal lattice of a compound is complex and difficult. Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for a series of related compounds. Certain molecular shapes and features favor the formation of crystals without solvent; these compounds tend to be stabilized by efficient packing of molecules in the crystal lattice, whereas other crystal forms are more stable in the presence of water and/or solvents. There may be too many possibilities so that no computer programs are currently available for predicting the crystal structures of hydrates and solvates. Vippagunta et. al. Advanced Drug Delivery Reviews 48 (2001) 3-26.

The scope of any compounds where the R variables are not those previously described above is not adequately enabled or defined. Applicants have provided no guidance as how the compounds are made more active *in vivo*.

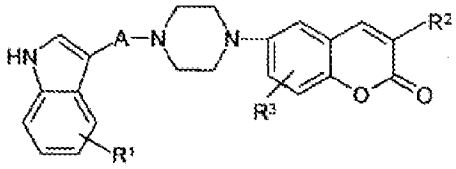
"Stereoisomers" literally would include thousands of additional compounds covered by the claims' scope that has the same molecular formula. In the absence of any guidance in the specification, nothing short of extensive synthesis and testing would be needed to determine if any such "isomeric" compound would have the activity needed to practice the invention.

3) *Number of working examples*. The compound core depicted with specific substituents represents a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples to enable the scope of the compounds instantly claimed or preventive agents. Applicant has provided no working examples of any

compounds, compositions or pharmaceutically acceptable salts where the R variables were not those mentioned above in the present application.

Within the specification, "specific operative embodiments or examples of the invention must be set forth. Examples and description should be of sufficient scope as to justify the scope of the claims. *Markush* claims must be provided with support in the disclosure for each member of the *Markush* group. Where the constitution and formula of a chemical compound is stated only as a probability or speculation, the disclosure is not sufficient to support claims identifying the compound by such composition or formula." See MPEP 608.01(p).

4) *Scope of the claims*. The scope of the claims involve all of the thousands of compounds of general formula I:



Thus, the scope of claims is very broad.

5) *Nature of the invention*. The application relates generally to chromenoneindole derivatives of the Formula I and finding novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

6) *Level of skill in the art*. The artisan using Applicants invention would be a chemist with a Ph.D. degree, and having several years of bench experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for making these compounds or compositions or treating the diseases mentioned.

5. Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition or a pharmaceutically acceptable salt thereof, does not reasonably provide enablement for any other compositions combined with “additional medicament active ingredients” not previously described. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

6. The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. (*United States v. Teletronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based on a single factor, but rather a conclusion reached by weighing many factors (See *Ex parte Forman* 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

1) *Amount of guidance provided by Applicant*. While the Applicant has demonstrated within the application how to make chromenoneindoles, applicant has provided no guidance, or provided any chemical or biological data and/or testing results of these particular compositions in combination with other "medicament active ingredients" containing this composition or a pharmaceutically acceptable salt thereof.

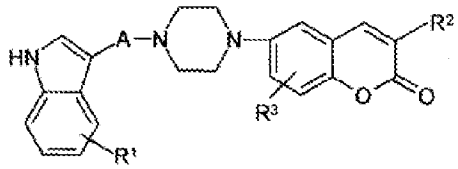
The quantity of experimentation needed to make or use the invention must be considered to determine if undue experimentation is present. Here applicants do not describe in any explicit detail what types of further active compounds have been combined with the compositions. As currently written, these "medicament active ingredients" could cover a plethora of various disciplines as the "medicament active ingredients" term is undefined.

2) Unpredictability in the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. (USPQ 18, 24 (CCPA 1970). See *In re Fisher*, 427 F.2d 833, 839, 166.

Applicants have provided no biological testing of any results where the compositions were combined with these additional "active compounds." Without this, one cannot simply infer that the results of the combination would be additive from the compositions or the active compounds alone. In many instances, the systematic screening of combinations of small molecules can reveal unexpected interactions between the pathways on which they act. (Borisy, et. al., Proceedings of the National Acadamy of Sciences of the United States of America, 100(13) 7977-7982.)

3) *Number of working examples*. The compound core depicted with specific substituents represent a narrow subgenus for which applicant has provided sufficient guidance to make and use; however, this disclosure is not sufficient to allow extrapolation of the limited examples of compounds to enable the scope of the compositions combined with additional medicament active ingredients. Applicant has provided no working examples of any compositions which have been combined with additional medicament active ingredients in the present application.

4) *Scope of the claims*. The scope of the claims involves all of the millions of compositions of the formula (I):



whereby the compound above is combined with any known “active medicament ingredient,” thus the scope of the claims is broad.

5) *Nature of the invention*. The application relates generally to chromenoneindole derivatives of the Formula I and finding novel compounds which have high bioavailability and are capable of significantly increasing the serotonin level in the brain.

6) *Level of skill in the art*. The artisan using Applicants invention would be a doctor with a M.D. degree, and having several years of professional experience.

MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the

time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here that Applicant is not enabled for treating the disease mentioned.

7. Claims 17 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for treating these specific human diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. The factors to be considered in making an enablement rejection have been summarized above.

Applicants do not state and it is not recognized in the CNS therapeutic arts these assays are correlated to clinical efficacy for the treatment of these human diseases. Applicants explain how to measure the binding to 5-HT_{1A} receptor but do not explain how to determine if the compounds activate (agonize) the two receptors after binding or deactivate (antagonize) the two receptors after binding. According to the specification, such measurements are essential to practicing the therapeutic claims. There are no assays describing the 5-$HT_{1D/2A/2C}$ receptors in the specification.

The state of the clinical arts in 5-HT_{1A} receptor related diseases is provided by Gaster (Ann Reports Med. Chem.) who states in the first complete paragraph on page 22 that “no clinical utility of 5-HT_{1A} receptor antagonists is known.” In the second

complete paragraph on page 21, Gaster (Ann Reports Med. Chem.) states that "Buspirone, which has utility as an anxiolytic agent, is an agonist at both pre-and post-synaptic 5-HT_{1A} receptor." The state of the clinical arts in D2 antagonist-related diseases is provided by Mortimer (Expert Opinion on Investigational Drugs). Mortimer (Expert Opinion on Investigational Drugs) states in the second complete paragraph, column 2, page 321 that "all antipsychotic drugs are D2 antagonists."

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the unknown scope of diseases embraced by the term "illnesses which are associated with the serotonin and dopamine neurotransmitter system and in which high-affinity serotonin receptors (5-5-HT_{1A} receptors) and/or dopamine DE receptors are involved." Thus, the scope of claims is very broad. MPEP §2164.01 (a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. Claims 1-11, 13-15 and 17-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 9 contain the phrase "or a …derivative…" in the claims. The language of Claim 1 and 9 is indefinite because there is no definition for the term "derivative" in the specification. One skilled in the art could construe the term "derivative" to mean numerous different things. Without a proper definition, one skilled in the art cannot possibly determine what is meant by "derivative." No new matter is permitted. Appropriate correction is necessary.

Conclusion

9. Claims 1-11, 13-15 and 17-19 are rejected.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey H. Murray whose telephone number is 571-272-9023. The examiner can normally be reached on Mon.-Thurs. 7:30-6pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisors, James O. Wilson can be reached at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey H Murray/
Examiner, Art Unit 1624

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624